

Peer Review File

Article information: <https://dx.doi.org/10.21037/tp-22-38>

Reviewer A

In the work by Liang et al titled “Management of pancreatic Kaposiform hemangioendothelioma with sirolimus in a pediatric patient: a case report and literature review” the authors present a case report of pancreatic KHE and summarize clinical findings related to similar cases treated with sirolimus. This is an interesting case and fairly well written review. However, there are a few concerns that could be addressed.

Abstract line 18 and line 220: The authors may want to consider adjusting the text to specify that KHEs can be locally aggressive. As this sentence is written it implies more malignant than is potentially warranted for KHE tumors.

Reply: We added “locally” before “aggressive” to make our expression more specific.

Changes in the text: see Page 1, line 19 and page 2, line 37. and page 3, line 47.

Background: The authors should introduce Kassabach-Merritt phenomenon (KMP) in the background section as this is a major complication for KHE even though it was not an issue for this case report. The authors should also further describe general KHE etiology, clinical course, treatment, and outcomes.

Reply: We have added a summary in the background part and further general introduction for KHE in discussion part.

Changes in the text: see page 3, line 53-56 and page 8, line 173-178, page 9, 181-185.

Line 119: This sentence should reference recent review by Kim et al. (Kim et al. Medicine (2021), PMID: 34918645).

Reply: We updated and added this recent review as the one of our references.

Changes in the text: see page 7, line 130

Table 1 and the case series analysis should include the case presented by Kim et al (2021), referenced above.

Reply: We added the case presented by Kim et al (2021) in table 1 and in our case series analysis.

Changes in the text: see page 7, line 138 (numbers of cases added one as this case was included) and table 1.

Line 146: The authors should more clearly describe the outcomes for the patients from the Cao et al. study. What is meant by good results?

Reply: We added the outcomes for patients as described in Yao W et al(2020)

Changes in the text: see page 8, line 157-158

Lines 150-157 should have some references cited.

Reply: We added some references in these lines.

Changes in the text: see page 8, line 168.

Line 174: ect. Should be replaced by et al., “et al.” should also be added to lines 134, 144, and 207.

Reply: We replaced all the mentioned lines by “et al.”

Changes in the text: see Page 7, line 144. Page 9, line 193. Page 11, line 231. and line 233.

Line 179-180 would benefit with a reference.

Reply: We tried to find references in long-term result of Whipple operation on a newborn but failed.

Changes in the text: No.

Line 185 needs a reference.

Reply: We added a reference in this line.

Changes in the text: see page 10, line 204.

Lines 195-200: Where is this treatment recommendation/experience coming from? A reference should be included for clarity.

Reply: We added a reference in this part for the experience of Sirolimus therapy described in Wang Z et al (2019).

Changes in the text: see page 11, line 221-227.

Line 207: Are the cases in the Ying et al. study pancreatic KHE or some other anatomic site, the authors may want to clarify as they are not in the table or case series.

Reply: We didn't include these two cases in our series because the involved anatomic site was not pancreas.

Changes in the text: None.

Line 213: What is meant by low quality of evidence? The authors may want to rephrase or remove this statement.

Reply: We removed this statement.

Changes in the text: see page 11, line 238.

Lines 209-211: The authors may want to include references to studies where patients have been treated with Long-term for long durations such as Chen et al. 2022 (PMID: 35083513).

Reply: Thank you for this question but we decided not to include references to studies in long-term sirolimus treatment. The reasons were as follow: 1. The follow-up duration was a little too short for evaluating the safety for a drug. For example, follow-up duration in most of the studies was 1 or 2 year, such as Chen et al. 2022 (PMID: 35083513) and Toshinori T et al.2016(PMID: 27513278). We noticed that Hu et al.2019 (PMID: 31429781) reported 32 patients with 4-year follow-up in 142 cases and they draw a conclusion in mild adverse events related to sirolimus, but the study lost 110 in 142 cases at the 4th year which made us doubt the reliability. 2. No studies in long-term safety of sirolimus treatment in KHE were reported. The tumor may have other effects on sirolimus treatment which needed more attention. 3. No studies in long-term result of sirolimus treatment in KHE were reported. The follow-up duration in most of the studies was 1 or 2 year. In conclusion, we still want to keep our former opinion on this section.

Changes in the text: None.

Discussion: The authors should include discussions of the mTOR pathway and rationale for sirolimus therapy for KHE in the first place. In this regard, some KHE and vascular tumor murine models could provide relevance of mTOR inhibition and models for preclinical testing. The authors may want to consider referencing: Sun et al. Cancer Cell 2015 (PMID: 26777415), Hanna et al. Journal of Pathology 2022 (PMID: 35066877), and Leech et al. Molecular Cancer Research 2014 (PMID: 25548102).

Reply: We added discussions of mTOR pathway and its' application on animal models and clinical treatment of KHE.

Changes in the text: see Page 10, line 205-210.

Table 1: the authors should include their reference number for each case (in addition to or rather than author name).

Reply: We added the reference number for each case in table 1.

Changes in the text: see table 1.

Table 1: The authors may want to expand the table for each case for clarity (as in the 3

cases from the Yao et al. study).

Reply: We expand the table for each case from the Yao et al. study.

Changes in the text: see table 1.

Table 1: The authors should include the cases reported in Kim et al. Medicine (2021), PMID: 34918645.

Reply: We added the case presented by Kim et al (2021) in table 1. (see table 1.)

Changes in the text: see table 1

Table 1: It is unclear what is meant by clinical diagnosis method. The authors should clarify or perhaps include biopsy, imaging, etc. to clearly define the diagnosis method.

Reply: We added an explanation for the term “clinical diagnosis” in table 1. (see table 1.) Histopathological diagnosis is the gold standard for KHE. Clinical diagnosis meant that those cases were diagnosed by imaging other than histopathological results, as it’s reported in Yao W et al(2020). This situation is mentioned in Page 8, line 154-160.

Changes in the text: see table 1.

Reviewer B

This is an interesting case report of KHE involving the pancreas and the clinical experience this team has had with response to Sirolimus. The case delivers an important message and is worth reporting given the rarity of this tumor in this anatomic location. The paper needs a lot of typographical and grammatical changes, I have done my best to address all of them in my review but there are inconsistencies in the spacing between words and parentheses along with multiple suggestions regarding changing the wording and adding additional details. All the suggested changes are in the form of comments within the attached PDF file.

1. Line 18 and line 37 and line 47: KHE is classified as a "borderline" tumor since they can be locally aggressive; however, they do not metastasize, using the word aggressive can be misinterpreted.

Reply: We added “locally” before “aggressive” to make our expression more specific.

Changes in the text: see Page 1, line 19 and page 2, line 37. and page 3, line 47

2. Line 24-26 and line 59-61 : This sentence would be better understood with another expression.

Reply: We agreed to change this sentence into “Additionally, a literature review of pancreatic KHE is provided to summarize the various experiences and individual treatments provided.”

Changes in the text: see Page 2, line 26-27 and page 3, line 62-64.

3. line 30-31: this sentence could be better understood by using the word “identified”.

Reply: We agreed to replace the word “disclosed” by “identified”, which could be better understood.

Changes in the text: see Page 2, line 31

4. line 35-36: What is the follow-up duration? it needs to be stated

Reply: We stated follow-up duration information of our case.

Changes in the text: see Page 2, line 35-37.

5. Line 50: Benign and "intermediate" are not the same, it is best to call it intermediate grade malignancy

Reply: We agreed to replace it by intermediate grade malignancy.

Changes in the text: see Page 2, line 48.

6. Line 57: better expressed by "be rare with"

Reply: We agreed to change it into "be rare with"

Changes in the text: see Page 3, line 58.

7. Line 73: delete "in department of medicine"

Reply: We agreed to delete it.

Changes in the text: see Page 3, line 77.

8. Line 75: Please list what other investigations were done.

Reply: We added detail information of the normal results.

Changes in the text: see page 4, line 79-82.

9. line 110: How long is the follow-up period so far? also what is the long term plan for following this patient up.

Reply: We added detail information of the postoperative result and follow-up details.

Changes in the text: see page 6, line 113-120.

10. Line 125: better expressed by "can result in"

Reply: We agreed to change it into "can result in"

Changes in the text: see Page 7, line 135.

11. line 129-130: better expressed by "pancreatic KHE involved the pancreatic head"

Reply: We agreed to rewrite this sentence.

Changes in the text: see Page 7, line 139-140.

12. line 134: "et al." after the author.

Reply: We replaced it by "et al."

Changes in the text: see Page 7, line 144.

13. line 138: better use "similar" here

Reply: We replaced it by "similar to"

Changes in the text: see Page 7, line 148.

14. line 146: report – case series

Reply: We replaced it by “case series”
Changes in the text: see Page 8, line 158.

15. line 147-148: confusing sentence: a radiological diagnosis and such initiation of therapy should be cautious and fully informed.

Reply: Thank you for the question. There is currently no guideline for KHE that can support treatment before histopathology diagnosis. Yao W et al(2020) reported success case series in Sirolimus treating suspected KHE cases before histopathology diagnosis in pediatric group. However, In China, we should be cautious in treating without a clinical guideline and initiate the treatment after their parents were fully informed. This is the meaning of the sentence and we hope that we’ve made it clear.

We change the word “evidence” into “clinical support by guideline” to make our expression more clear

Changes in the text: see Page 8, line 159-160.

16. line 150: change “histologic pathology” into “histopathology”

Reply: We changed it by “histopathology”

Changes in the text: see Page 8, line 160.

17. line 161: change “is” into “was”

Reply : We changed it by “was”

Changes in the text: see Page 8, line 172.

18. line 163: change “be involved” into “occur”

Reply: We changed it by “occur”

Changes in the text: see Page 9, line 178-179.

19. line 168-169: question: “5 out of 8 is 62% of the cases, this is not significantly lower and can be misleading.”

Reply: We rechecked the numbers and found there were 5 cases suffered KMP out of 10 total cases in our series including our case, which made the percentage to 50% and significantly lower than the reported 70%.

Changes in the text: see Page 9, line 187.

20. line 173: change “good way to choose” into “reasonable treatment choice.”

Reply: We changed it by “reasonable treatment choice”

Changes in the text: see Page 9, line 192-193.

21. line 174: “et al.” after the author.

Reply: We added “et al.”

Changes in the text: see Page 9, line 193.

22. line 175: hypothermocytois is not a clinical term

Reply: We replaced it by “thrombocytopenia”

Changes in the text: see Page 9, line 194.

23. line 175: correct term for “frozen section pathologic examination”

Reply: We replaced it by “frozen section pathologic examination”

Changes in the text: see Page 9, line 195.

24. line 187: better use “with” here

Reply: We replaced it by “with”

Changes in the text: see Page 10, line 212.

25. line 187: here should be “patients”

Reply: We replaced it by “patients”

Changes in the text: see Page 10, line 213.

26. line 189: what is the meaning of the word “Soften” here.

Reply: Soften of the tumor was cited according to Wang Z et al.(2019), which represented the lesion showing a response to the therapy. To be specific, “Soften” meant a good result although the result was not good enough to show shrinkage of the lesion in this article.

Changes in the text: see Page 10, line 214-215.

We added the reference of Wang Z et al. (2019) here to show that Soften of the tumor was cited and as an evidence for good result in the article.

27. line 191-193. This statement sounds like self referencing, it is best to change it to "In a case series tumor shrinkage post sirolimus therapy was seen in 5 out of 6 patients (including one case showing no response to steroids and vincristine at first). " No need to go through the details of the two excluded patients.

Reply: We tried to express our opinion better with a new expression.

Changes in the text: see Page 11, line 216-220.

28. line 204 and 207: “et al.” after the author.

Reply: We added “et al.”

Changes in the text: see Page 11, line 231. and line 233.

29. line 215: better expressed by “guidance”

Reply: We replaced it by “guidance”

Changes in the text: see Page 12, line 240-241.

30. line 302: better expressed by “visualized”

Reply: We replaced it by “visualized”

Changes in the text: see Page 16, line 365.

31. line 323: The D2-40 and Prox-1 stains are showing "peripheral lymphatic staining"

not just staining, this actually is a helpful feature in confirming KHE in which the lymphatic channels tend to stain at the periphery of the nodules and not the entire proliferation.

Reply: We tried to express better with a new expression.

Changes in the text: see Page 17, line 382-384.

32. table 1: please reference each author so the reader can go to original manuscript if needed.

Reply: We added the reference each author.

Changes in the text: see table 1.

33. table 1: change “histologic pathology” into “histopathology”

Reply: We changed it by “histopathology”

Changes in the text: see table 1.

34. table 1: change “adapted” into “secondary”

Reply: We changed it by “secondary”

Changes in the text: see table 1.

35. table 1: change “result” into “follow-up”

Reply: We changed it by “follow-up”

Changes in the text: see table 1.

36. table 1: change “demised” into “deceased”

Reply: We changed it by “deceased”

Changes in the text: see table 1.